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Secondary sclerosing cholangitis in critically ill patients: an underdiagnosed entity

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Secondary sclerosing cholangitis in critically ill patients: an underdiagnosed entity

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Orientado por:

Prof. Dr.ª Mariana Verdelho Machado

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Abstract: Secondary sclerosing cholangitis in critically ill patients (SSC-CIP) is a recently identified cholestatic liver disease occurring in patients without prior history of hepatobiliary disease, after receiving treatment in the intensive care unit (ICU) in different sets, including: cardiothoracic surgery, infection, trauma and burns. It is a rare entity, being estimated to occur in one in 2000 patients in an ICU, however it is a dismal condition with up to half of the patients dying during the ICU stay and with rapid progression to liver cirrhosis over weeks to months. SSC-CIP should be considered in the differential diagnosis of cholestasis in the ICU, particularly when cholestasis persists after recovery from the critical event. Diagnosis is established with magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) showing dilations and stenoses of the intrahepatic bile ducts, as well as biliary casts. No available treatment has been shown to slow the rapid progression of the disease, and liver transplant referral should be considered early after the diagnosis of SSC-CIP. Increased awareness and timely diagnosis are crucial in order to improve the current appalling outcome.

Keywords: secondary sclerosing cholangitis, critically ill patients, intensive care, biliary casts, bile casts

Resumo: A colangiopatia associada aos cuidados intensivos (CACI), descrita pela primeira vez em 2001, é uma doença colestática que ocorre em doentes sem antecedentes de patologia hepatobiliar após internamento na Unidade de Cuidados Intensivos (UCI). As indicações que motivaram a necessidade de UCI podem ser: após uma cirurgia major (particularmente cardiotorácica), infeção, trauma e queimaduras [1, 2]. A prevalência exacta da doença não é conhecida mas estima-se que ocorra em 1 em cada 2000 doentes na UCI [3, 4]. A duração do internamento em UCI é em média 30-40 dias, a idade média dos doentes é 50 anos. Factores de risco conhecidos são o sexo masculino, necessidade de ventilação mecânica e episódios de hipotensão grave durante o internamento [5, 6]. Obesidade e aumento da gordura visceral, bem como maior tempo passado em posição de decúbito ventral são também outros factores de risco descritos para desenvolver CACI [7].

A fisiopatologia ainda não é completamente conhecida, mas tanto a doença crítica como o seu tratamento em UCI parecem estar implicados. A hipótese mais aceite defende que há um insulto isquémico primário (**"colangiopatia isquémica"**), que em conjunto com alterações da composição da bílis (**"bílis tóxica"**) leva à necrose de colangiócitos, principalmente a nível intra-hepático, com formação de cilindros biliares e estenoses [2, 3, 8]. A obstrução biliar

resultante favorece a infeção biliar persistente que acelera a destruição progressiva e irreversível dos canais biliares intra-hepáticos, cujo resultado final é a cirrose biliar secundária [9].

São vários os argumentos a favor do conceito de "colangiopatia isquémica" como mecanismo fisiopatológico primário: 1) os ductos biliares intra-hepáticos são mais suscetíveis à isquémia do que o parênquima hepático e o colédoco, em virtude da sua vascularização exclusivamente derivada de ramos da artéria hepática [10, 11]; 2) nos doentes que desenvolvem CACI, a ocorrência de instabilidade hemodinâmica é duas a 3 vezes mais frequente do que nos doentes internados em UCI no geral [9, 12, 13]; 3) o início da hipotensão relaciona-se temporalmente com o aparecimento de colestase [3]; 4) todos os doentes com CACI receberam ventilação mecânica, que se associa a diminuição do fluxo sanguíneo hepato-esplâncnico [6, 14, 15]; e 5) os cilindros biliares estão presentes desde as primeiras semanas após o início da colestase e a sua composição rica em proteínas reflecte a necrose de colangiócitos [9, 16]. Por outro lado, o uso de vasopressores em doses altas não parece promover o desenvolvimento de CACI.

Tanto a isquémia como a inflamação sistémica são responsáveis pela diminuição da expressão de transportadores hepatobiliares, nomeadamente MDR3 e AE2, o que altera a composição da bílis tornando-a mais tóxica e contribuindo para a necrose de colangiócitos [17-19]. Admite-se que variantes genéticas associadas à diminuição da expressão destes transportadores confiram risco acrescido de desenvolver CACI [8].

A infeção biliar por organismos multi-resistentes como *Enterococcus* e *Candida albicans,* facilitada pela obstrução biliar, é responsável por colangites recorrentes. As colangites não parecem contribuir para o desenvolvimento de CACI, mas relacionam-se com a progressão para cirrose biliar [2, 9, 20].

Por outro lado, a **colangiopatia induzida por fármacos**, um subtipo de lesão hepática induzida por fármacos que se manifesta por um padrão analítico do tipo colestático, é uma causa de colangite esclerosante secndária (CES) e pode ser um fator promotor de CACI em doentes geneticamente suscetíveis. Os fármacos mais implicados são os antibióticos e agentes anestésicos como a cetamina [21-24]. A **nutrição parentérica total**, apesar de se associar a disfunção hepática com esteatose e colestase, não parece ter um papel importante no desenvolvimento CACI [3, 25].

O diagnóstico de CACI é difícil por várias razões: 1) ainda é uma entidade pouco reconhecida; 2) é assintomática nas fases iniciais, manifestando-se apenas como um padrão colestático nas provas hepáticas; 3) o diagnóstico diferencial de colestase na UCI é vasto, sendo secundária a CACI apenas numa minoria dos casos; 4) o diagnóstico definitivo só pode ser estabelecido por colangiopancreatografia por ressonância magnética (CPRM) ou colangiopancreatografia retrógrada endoscópica (CPRE); e 5) a mortalidade durante o tratamento na UCI é elevada, muitas vezes não permitindo um diagnóstico atempado [2, 13, 26].

Laboratorialmente, observa-se uma elevação inicial da gama-glutamil-transpeptidase (GGT) durante a segunda semana após o evento potencialmente fatal, seguida pela elevação da fosfatase alcalina (FA). Só mais tarde se verifica a elevação da bilirrubina, sendo que a aspartato aminotransferase (AST) e a alanina aminotransferase (ALT) permanecem normais ou pouco elevadas. O pico da GGT é mais pronunciado que o da FA e da bilirrubina [2, 27]. Nesta fase, o diagnóstico diferencial inclui: colestase induzida por sépsis, nutrição parentérica total, coledocolitíase, lesão hepática induzida por fármacos e lesão hepática isquémica. A persistência de colestase mesmo após melhoria clínica é o principal aspecto que distingue a CACI das outras entidades [28, 29].

A ecografia abdominal é frequentemente o método inicial de avaliação imagiológica da colestase, mas tem uma baixa sensibilidade para a deteção de CACI, pelo que uma ecografia normal não deve excluir outros exames quando há suspeita clínica (i.e. quando a colestase persiste ou o doente desenvolve colangite) [2]. O diagnóstico é confirmado por CPRM ou CPRE que, na fase inicial, revelam cilindros biliares nos canais biliares intra-hepáticos. Em fases mais avançadas há estenoses e dilatações difusas dos canais biliares intra-hepáticos, com obliteração progressiva dos ductos periféricos. As vias biliares extra-hepáticas estão poupadas em 80% dos casos [2, 27, 30]. O diagnóstico é frequentemente tardio, demorando em média 60 dias nos estudos iniciais, sendo que estudos mais recentes reportaram um atraso de 25 dias desde o início da colestase até ao diagnóstico [4, 30, 31]. Este atraso traduz não só a falta de reconhecimento da doença, mas também a dificuldade em aferir quais os doentes que vão beneficiar da CPRM/CPRE [29, 30]. O exame histológico tem um papel reduzido no diagnóstico, revelando apenas achados inespecíficos de obstrução biliar crónica, sendo, no entanto, útil para o diagnóstico diferencial ao excluir outras patologias [9, 32].

A história natural da doença contempla duas fases distintas. Uma fase inicial assintomática, marcada apenas pela colestase em provas hepáticas. Ainda assim a mortalidade destes doentes durante o tratamento na UCI é de 50% e associa-se a necessidade de terapêutica de substituição renal e pontuações MELD mais elevadas [27, 30]. A condição que motivou o internamento na UCI também influencia o prognóstico: trauma e queimaduras associam-se a menor mortalidade, por poderem ocorrer em pessoas previamente saudáveis [33]. A segunda fase só é aparente no doentes que sobrevivem ao tratamento na UCI e é dominada pelos sintomas típicos de colangite esclerosante: icterícia, prurido e desconforto abdominal [29]. Na maioria dos doentes também se verifica acentuada perda ponderal e o curso da doença é muitas vezes complicado por episódios recorrentes de colangite bacteriana [2, 34]. A evolução da doença é dramática, podendo progredir para cirrose hepática em meses [13]. Consequentemente, a mortalidade é muito elevada, apresentando uma sobrevida livre de transplante mediana de 13-44 meses, significativamente inferior à de colangite esclerosante primária e colangite esclerosante secundária no geral [2, 34, 35]. Cerca de 40% dos doentes morre de insuficiência hepática, 40% desenvolve cirrose biliar secundária mas mantém-se estável e 20% progride para doença hepática terminal com necessidade de transplante [5].

As opções terapêuticas na CACI são limitadas. A remoção endoscópica de cilindros biliares e esfincterotomia levam a uma melhoria clínica e bioquímica transitória, mas não evitam a progressão nem alteram o prognóstico dos doentes [9, 34, 36]. O ácido ursodesoxicólico é frequentemente utilizado, mas não parece ter eficácia [13, 37]. Os episódios recorrentes de colangite são tratados com terapêutica endoscópica e antibioticoterapia, que deve ser dirigida com base no exame microbiológico da bílis e prolongada por duas semanas [6, 38]. O transplante hepático é a única terapêutica curativa, sendo que 75% dos doentes com CACI são colocados em lista de espera para transplante hepático no primeiro ano após o diagnóstico. A sobrevida após transplante é de 90% a 1 ano e 85% a 3 anos, comparável à dos doentes transplantados por cirrose hepática alcoólica [2, 33]. A maioria das mortes após transplante ocorrem no primeiro ano, sendo a sépsis a principal causa de morte [31].

Em conclusão, a CACI é uma doença ainda pouco reconhecida e subdiagnosticada, para a qual não existe tratamento médico eficaz, sendo o tratamento endoscópico apenas paliativo. Tendo em conta o terrível prognóstico desta doença, a única forma de melhorar a sobrevida dos doentes é o diagnóstico atempado com referenciação precoce para transplantação hepática.

Palavras-chave: colangite esclerosante secundária, colangiopatia, cuidados intensivos, cilindros biliares

List of abbreviations

ABCB4: ATP-binding cassette 4

AE2: Anion exchanger 2

ALP: Alkaline phosphatase

ALT: Alanine aminotransferase

ARDS: Acute respiratory distress syndrome

AST: Aspartate aminotransferase

DILI: Drug-induced liver injury

GGT: Gamma glutamyl transpeptidase

HLI: Hypoxic liver injury

ICU: Intensive care unit

MELD: Model for End-Stage Liver disease

MDR3: Multidrug resistance protein 3

NOD2: Nucleotide binding oligomerization domain containing 2

OLT: Orthotopic liver transplantation

PEEP: Positive end-expiratory pressure

PSC: Primary sclerosing cholangitis

RBC: Red blood cell

SIRS: Systemic inflammatory response syndrome

SSC-CIP: Secondary sclerosing cholangitis in critically ill patients

TPN: Total parenteral nutrition

UDCA: Ursodeoxycholic acid

ULN: Upper limit of normal

Conteúdo

Introduction

Sclerosing cholangitis encompasses a group of progressive cholestatic diseases affecting the intrahepatic and/or extrahepatic bile ducts that can progress to biliary cirrhosis. Primary sclerosing cholangitis (PSC) is an idiopathic disease characterized by a typical beaded appearance in cholangiographic studies, for which no effective medical treatment is available. PSC has a strong association with inflammatory bowel disease. [39, 40]. When we can identify a cause for sclerosing cholangitis it is dubbed secondary sclerosing cholangitis (SSC). Examples of SSC are auto-immune IgG4-associated, infectious, drug-induced, ischemic and obstructive [41]. SSC in critically ill patients (SSC-CIP) is a rare form of SSC that was first described by Scheppach *et al.* in 2001 [1]. SSC-CIP is believed to be ten times less frequent as PSC [2]. Only 250 cases were reported in the literature. Over half of the cases were published in the last 5 years, which reflects increasing recognition of SSC-CIP as a cause of hepatic dysfunction in the intensive care unit (ICU).

SSC-CIP affects patients with no history of previous hepatic/biliary disease, after treatment in an ICU for a variety of different underlying conditions including major surgery, sepsis and trauma [2, 30]. The pathogenesis of SSC-CIP is still not fully understood, however ischemia of the bile ducts is widely regarded as the primary mechanism. Changes in bile composition and subsequent biliary infection also seems to play a role [3, 9, 27]. Cholestasis is a common finding in critically ill patients, affecting up to 20% at admission in the ICU and it is usually reversible when associated with sepsis, drug-induced hepatotoxicity, parenteral nutrition or other forms of SSC [26, 42]. However, when cholestasis persists beyond the successful treatment of the underlying disease, we should suspect of SSC-CIP [9]. The diagnosis is made by endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) revealing PSC-like diffuse strictures and dilations of the intrahepatic bile ducts, and filling defects translating biliary casts [13, 27]. Biliary casts are present since the early stages of the disease [2, 9]. SSC-CIP typically has two different presentations: 1) acute liver failure during ICU treatment, often leading to death while patients wait for liver transplantation, or 2) persistent cholestasis rapidly progressing to cirrhosis [9, 30, 43, 44]. The prognosis is dire, with around half the patients dying in the ICU,

and the other half requiring liver transplantation in the following 3-4 years [2, 33]. Despite increased recognition in recent years, SSC-CIP remains underdiagnosed. In the cases where SSC-CIP is identified, the median time from the first signs of cholestasis to diagnosis is 54 days, mostly due to a delay in performing ERCP [2].

This review aims to summarize the most recent evidence regarding the pathogenesis, diagnosis and prognosis of SSC-CIP. An emphasis is placed on differential diagnosis to help in the early recognition of these patients, which might improve outcomes, allowing earlier palliative endoscopic therapy and earlier referral for liver transplantion.

Epidemiology

Critically ill patients who develop SSC are a very heterogeneous group owing, in part, to the variety of possible underlying diseases that lead them to the ICU. The unifying feature is the lack of history of hepatobiliary disease prior to the life-threatening event, a prerequisite for the diagnosis [2, 4, 37].

Reasons for admission in the ICU include burns, trauma, acute respiratory distress syndrome (ARDS), infections, subarachnoid haemorrhage, and post major surgery [2, 4, 13, 32]. Cardiothoracic surgery seems to confer a particularly high risk of developing SSC-CIP [30, 34]. The mean age of patients at the time of diagnosis is 50 years, but ranges from 19 to 79 years, which can be explained by the unpredictable nature of some of the reasons for admission in the ICU [5, 9]. The average length of stay in ICU is 30-40 days, though in some cases as short as 9 days [2, 43, 45]. Similarly to PSC, males seem to be more prone to SSC-CIP than females with studies reporting a male/female ratio ranging from 2.2:1 to 9:1 [3, 4, 9, 27, 32, 46]. All reported patients required mechanical ventilation during their stay in ICU for an average of more than 30 days and most patients presented severe hypotension requiring vasopressor treatment [3-6, 9]. Weig *et al.* evaluated patients with ARDS due to H1N1 pneumonia and found that obesity, increased visceral fat and longer time spent in prone position were associated with a higher risk for developing SSC-CIP [7].

Although certainly rare, the true prevalence of SSC-CIP has not been ascertained. In fact, SSC-CIP is an underdiagnosed condition, with half of the patients dying during ICU stay, before the diagnosis can be reached [30, 33]. Any attempt would probably underestimate it, as it remains underdiagnosed. Two retrospective studies found similar prevalence of SSC-

CIP, affecting about 1 in 2000 patients admitted in an ICU [3, 4]. Leonhardt *et al.* identified SSC-CIP as being responsible for 0.61% of all liver transplants in one hospital, which was 10 times less frequent as PSC accounting for 6.2% [2].

Pathophysiology

The exact mechanisms by which SSC-CIP develops are yet to be understood. Both critical illness and its intensive care treatment seem to contribute to the pathogenesis [3]. The most accepted theory is that ischemia (**"ischemic cholangiopathy"**) in combination with changes in bile composition (**"toxic bile"**) lead to necrosis of cholangiocytes and bile cast formation. The resulting biliary obstruction and biliary infection all participate in a process that leads to progressive and irreversible destruction and obliteration of the intrahepatic bile ducts, ultimately leading to secondary biliary cirrhosis [2, 3, 8, 9, 36].

Other factors of modern intensive care treatment might play a role in the pathogenesis of SSC-CIP [9]. **Total parenteral nutrition** (TPN) is common in critically ill patients and can lead to steatosis and cholestatic liver dysfunction when used for more than one week [25, 28]. However, epidemiological studies do not support TPN as a risk factor for SSC-CIP, since in a series of 16 patients by Leonhardt *et al.*, patients either did not receive TPN prior to the onset of cholestasis, or received for only a short period [3].

Idiosyncratic **drug-induced liver injury** (DILI) could also play an important role in the development of SSC-CIP. When DILI manifests as a cholestatic or mixed type pattern in hepatic tests it is referred to as drug-induced cholangiopathy, reflecting damage of the biliary epithelium. Patients with drug-induced cholangiopathy can develop SSC [21, 22]. Several drugs commonly used in the ICU setting have been implicated in drug-induced SSC including antibiotics and anaesthetics such as ketamine [22, 24, 47]. Interestingly, in one case series 15 out of 16 patients received ketamine prior to developing SSC-CIP [3]. Lastly, genetic predisposition is likely a key determinant to developing drug-induced cholangiopathy [23].

- **Ischemic cholangiopathy**

The hepatic parenchyma is supplied by both the hepatic arteries and the portal vein, whereas the common bile duct receives a dual arterial blood supply from both the hepatic artery and branches of the gastroduodenal artery [48]. However, the intrahepatic biliary tree is supplied exclusively by branches of the hepatic artery, which form the intrahepatic peribiliary vascular

plexus [10, 11]. This provides the anatomical grounds for intrahepatic bile duct ischemic susceptibility and could explain why the extrahepatic bile duct is usually spared in SSC-CIP [2, 13, 27].

Macrocirculatory compromise seems to be the cornerstone of ischemic bile duct injury, particularly when associated with microcirculatory disturbances directly affecting the peribiliary vascular plexus [3, 11]. Around 33% of ICU patients have hemodynamic instability requiring vasopressors at any time during their stay [12]. In patients who go on to develop SSC-CIP, this number rises to 60-100% [3, 9, 13]. Moreover, the onset of hypotension seems to temporarily associate with the onset of cholestasis [3]. Previous researchers have hypothesized that the use of **high-dose vasopressors** could promote the development of SSC-CIP [4, 6, 9, 13]. However, this hypothesis is not consubstantiated by the available data, and because of the relevance of vasopressors in the ICU setting, this is a matter that needs a thorough discussion. The optimal use of vasopressors in shock is still controversial, being norepinephrine and dopamine the most commonly used [12]. All vasopressors and inotropes increase systemic blood pressure and cardiac output, but this does not necessarily translate into improved hemodynamics in the hepatosplanchnic territory [49]. Norepinephrine, based on its α-adrenergic agonist effects, has been assumed to induce splanchnic ischemia. However, the experimental data is hard to interpret because studies are very heterogeneous regarding their population and hemodynamic endpoints [49]. For example, norepinephrine has been shown to have no effect on mesenteric blood flow in a septic sheep model, however it decreased mesenteric blood flow in a septic porcine model [50, 51]. In one study with 10 septic human patients, norepinephrine associated with a higher hepatosplanchnic blood flow to cardiac output ratio as compared with dopamine, resulting in improved hepatocellular energy balance [52]. This result was unexpected since regional vasodilating properties of dopaminergic activation should lead to a higher hepatosplanchnic to cardiac output ratio in the dopamine treated patients. These findings translate the contradictions found in the literature, as well as the unreliability of biological plausibility as the sole argument for vasopressor-induced biliary ischemia. More recently, two small retrospective studies failed to demonstrate an association between high-dose vasopressor use and higher risk for SSC-CIP development [3, 7].

All patients with SSC-CIP received mechanical ventilation, which is believed to contribute to hepatosplanchnic ischemia [5, 6]. In fact, mechanical ventilation with positive end-expiratory pressure (PEEP) higher than 10cm H_2O, prone positioning and low tidal volumes associated

with negative effects on the hepatosplanchnic blood flow, in animal models [14, 15, 53]. Prone positioning in particular seems to be associated with the development of SSC-CIP, in humans [7].

Leonhardt *et al.* showed that all SSC-CIP patients presented at least one factor capable of disrupting the microcirculation blood flow, namely increased blood viscosity, red blood cell (RBC) transfusions and/or hypercoagulable states [3]. Moreover, two different groups also suggest an association between higher RBC units transfused and an increased risk for SSC-CIP development [13, 27].

In summary, disturbances in the arterial supply of the peribiliary vascular plexus lead to necrosis of cholangiocytes with formation of biliary casts and inflammation/scarring of the bile ducts which results in cholestasis [9, 34]. A different set where biliary casts have been extensively described is following orthotopic liver transplantation (OLT), in which two different types of biliary casts have been identified based on their biochemical composition. One type is mainly composed of bilirubin (10-50%) and bile acids (10-15%) and is thought to arise due to mechanical obstruction. The other type is mainly composed of proteins, mostly collagen, which seems to be derived from necrotic cholangiocytes [16, 54]. Biliary casts in SSC-CIP are mainly composed of proteins and can be seen in the first weeks after the onset of cholestasis, further hinting at the role of ischemia as the primary insult in these patients [9].

- **Toxic bile**

Cholangiocytes, even under physiological circumstances, are exposed to toxic concentrations of hydrophobic bile salts. To survive in such an environment requires defence mechanisms that rely on hepatobiliary transporters. The formation of mixed micelles of bile salts is one such mechanism and it is dependent on biliary phospholipid secretion by hepatocytes via MDR3/ABCB4 [8, 55]. Genetic defects with impaired MDR3/ABCB4 activity have been linked to cholestatic and ductopenic liver disease in humans [56]. It has been shown that MDR2 (human orthologue - MDR3) knockout mice develop sclerosing cholangitis secondary to the complete absence of phospholipids from bile [17, 57]. Ischemia has also been shown to negatively affect hepatobiliary transporters and lead to cell injury and cholestasis [18, 58]. Trauner *et al.* have theorized that low expression MDR3 genetic variants might predispose to the formation of toxic bile under ischemic or inflammatory conditions, thus playing an important role in determining which critically ill patients with cholestasis go on to develop

SSC-CIP [8]. Another important mechanism of defence is the secretion of HCO_3^- via AE2, which maintains a high pH near the apical surface of cholangiocytes, capable of preventing permeation of protonated bile acids. Beuers *et al.* theorized that loss of this protective mechanism due to ischemia is implicated in SSC-CIP [55]. Indeed, pro-inflammatory cytokines inhibit AE2 activity in animal models [19].

Inflammatory cytokines play an integral role in the pathophysiology of systemic inflammatory response syndrome (SIRS). The incidence of SIRS has been estimated as being over 50% in ICU patients [59]. Leonhardt *et al.* found that all 16 of their SSC-CIP patients developed SIRS prior to the diagnosis [3]. These findings suggest that ischemia is responsible not only for direct damage to cholangiocytes, but also, in conjunction with inflammatory stress, for the development of toxic bile that further contributes to cholangiocyte necrosis.

- **Biliary infection**

Few case reports described SSC following a single severe episode of bacterial cholangitis, however it is much more frequent the development of SSC after recurrent bacterial cholangitis in the context of chronic biliary obstruction. [29, 60].

Biliary obstruction is a prerequisite for bacterial cholangitis because it abrogates the antibacterial effects of bile flow and the biliary secretion of IgA [38]. In SSC-CIP, biliary obstruction is the result of the development of biliary casts, which are present since the first weeks of cholestasis. As the disease progresses, the obstruction is perpetuated due to the development of multifocal intrahepatic biliary strictures [2, 9]. A meta-analysis found that bacteria and/or *Candida* species are detectable in the bile collected during ERCP in 98% of SSC-CIP patients [6]. Enterococci and *Candida albicans* are the most common agents, which frequently present a high rate of antibiotic resistance, presumably a reflection of the high rate of previous antibiotic treatment in critically ill patients [20]. Recurrent bacterial cholangitis is common in SSC-CIP patients, and while it is yet to be determined if it is itself pathogenic or an innocent bystander, infection associates with the progression to cirrhosis [2, 6, 9, 45]. The role of the microbiota is also highlighted by the recently described association between NOD2 gene mutations and higher susceptibility for developing SSC-CIP [61]. NOD2 is a pattern recognition receptor that regulates the gut-microbiome homeostasis and has a key role in bacterial translocation. NOD2 gene mutations had already been identified as risk factors for Crohn's disease and spontaneous bacterial peritonitis in patients with liver cirrhosis [61, 62]. **The pathophysiology of SSC-CIP is summarized in Figure 1.**

Diagnosis

The diagnosis of SSC-CIP is difficult for several reasons: 1) it is still a greatly underrecognized entity; 2) it is asymptomatic in the early stages, manifesting only as a cholestatic pattern in liver tests; 3) the differential diagnosis of cholestasis in ICU patients is vast, being secondary to SSC-CIP in only a minority of these patients; 4) the diagnosis can only definitively be established by MRCP/ERCP; and 5) mortality is high during ICU treatment often not allowing a timely diagnosis [2, 13, 26].

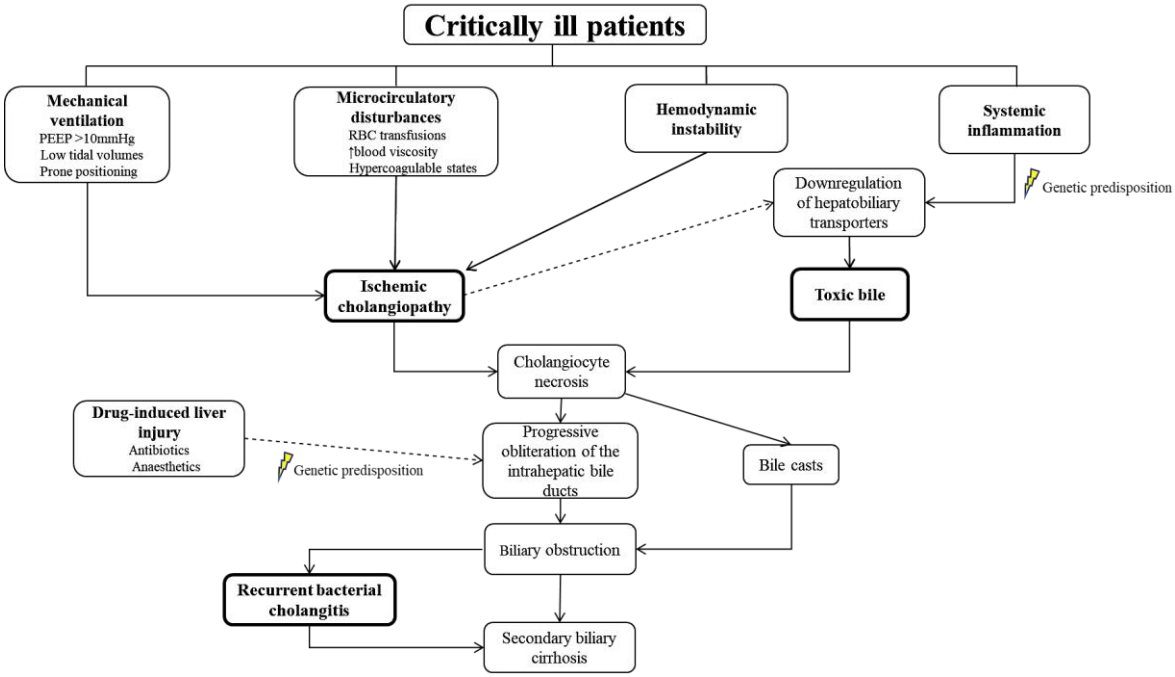

Figure 1. Schematic representation of the pathophysiology of SSC-CIP.

- **Laboratory parameters**

SSC-CIP manifests with a pattern of elevation of cholestatic parameters. Gamma glutamyl transpeptidase (GGT) rises first, around 7-9 days after the initial insult and is followed, a few days later, by alkaline phosphatase (ALP) elevation. Bilirubin is the last one to rise, taking around 20 days. GGT is also more pronounced, peaking at around 20-50 times the upper limit of normal (ULN), while ALP and bilirubin elevation reach a maximum of 15 times the ULN [2, 27]. Conversely, ALT and AST show only a moderate increase of up to 3 times the ULN [5]. Interestingly, bilirubin levels may spontaneously decrease after 2-6 months while SSC-CIP keeps progressing [13]. In one study there was a significant increase of cholesterol levels in SSC-CIP patients, around 2.5 times the ULN, differentiating it from PSC, in which hypercholesterolemia is uncommon [2, 63].

The differential diagnosis for cholestasis in the ICU set is extensive, most notably: sepsis-induced cholestasis, TPN, choledocholithiasis**,** and DILI [26, 28]. Hypoxic liver injury (HLI), although mostly characterized by hepatocellular necrosis, still merits discussion. Indeed, HLI affects 10% of ICU patients, it also associates with shock states and manifests as jaundice in one-third of patients [42]. **The different characteristics of these diseases are shown in Table 1.**

The single most important aspect that distinguishes SSC-CIP from the other causes is cholestasis persisting beyond clinical recovery. Persistent cholestasis reflects irreversible anatomical damage rather than transient functional impairment [28, 29].

- **Imaging studies**

The first diagnostic study in a patient with cholestasis is an abdominal ultrasound, which can rule out other diagnosis such as choledocholithiasis, although lacking sensitivity for SSC-CIP [64]. Indeed, abdominal ultrasound suggested the diagnosis of SSC-CIP in only 30% to 40% of patients [2, 30]. This low sensitivity is due to the fact that echogenic biliary casts are present since the first weeks of cholestasis and they assume the shape of the biliary tree, mimicking a normal bile duct system. Hence, a normal abdominal ultrasound should not exclude further testing when SSC-CIP is suspected (i.e. when cholestasis persists beyond recovery from the ICU or cholangitis develops) [30].

MRCP is the imaging method of choice following abdominal ultrasound and prior to ERCP since it is non-invasive and can accurately diagnose SSC-CIP. In the early stages of the disease MRCP reveals defects in the intrahepatic biliary tree corresponding to biliary casts and biliary leakages, occasionally forming bilomas. At later stages diffuse intrahepatic bile duct strictures are observed. Notably, the distal common bile duct is preserved at all stages [27]. MRCP has some disadvantages compared to ERCP in SSC-CIP. Most notably, it does not allow for interventional procedures. Furthermore, MRCP is also limited in patients with heart medical devices, which are relatively common in SSC-CIP patients [30].

ERCP is considered the gold standard for the diagnosis of SSC-CIP [2, 4, 9, 13]. Despite the marked cholestasis, ERCP is often delayed with most studies reporting a delay of around 60 days until it is performed, though more recent studies reported lower delay up to 25 days [2, 4, 30, 31]. This delay might be attributable to several factors: 1) there is still lack of awareness of SSC-CIP; 2) dilated bile ducts on ultrasound (that would prompt the realization

of ERCP) occurs in less than 50% of the cases; and 3) SSC-CIP is seldom misdiagnosed as sepsis-induced cholestasis (the most common cause of cholestasis in the ICU) [2, 29, 65]. As such, often, it is not until cholestasis fails to resolve after clinical recovery that the clinical suspicion of SSC-CIP becomes significant enough to merit an invasive test such as ERCP, inevitably leading to a delayed diagnosis [29, 30].

Table 1. Differential diagnosis of SSC-CIP in the ICU setting.

Diagnosis	Incidence in ICU patients	Clinical features and laboratory tests	Diagnosis	Treatment	Prognosis	References
Sepsis-induced cholestasis	20% (most common cause of cholestasis in the ICU)	Sepsis (mostly gram-negative). Biphasic pattern: initial elevation of ALT/AST, followed by elevation of bilirubin. ALP and GGT may be normal.	Biphasic laboratorial pattern in the setting of positive blood cultures (usually gram-negative).	Aggressive antimicrobial treatment. Circulatory and ventilatory support.	Two-fold increase in mortality comparing to sepsis alone. Cholestasis is reversible.	[28, 66, 67]
TPN associated cholestasis	3%	TPN >1 week, RUQ and hepatomegaly. Mixed pattern with cholestasis and hepatocellular necrosis.	Cholestasis in the setting of TPN after exclusion of other causes.	Avoidance of excessive calories and appropriate dosing and formulation of lipids. Discontinuation or cycling of TPN if feasible.	Liver dysfunction is self-limited but may progress to steatohepatitis and cirrhosis if TPN >6months.	[25, 28]
Choledocholithiasis	-	RUQ pain accompanied by nausea and vomiting. Rise in ALT/AST followed by ALP and bilirubin. INR may be elevated. Transient.	US and CT scan may reveal dilated bile ducts and duct stones in the initial evaluation. Diagnosis is usually confirmed by MRCP or EUS.	ERCP with sphincterotomy and stone extraction.	Benign, but may complicate with acute pancreatitis and bacterial cholangitis.	[64, 68]
DILI	-	Idiosyncratic drug reaction (commonly antibiotics and anaesthetics). Hepatocellular, cholestatic or mixed pattern. Cholestatic pattern more common in >60 years old, associated with antibiotics.	Establishment of causal relationship according to clinical scores such as RUCAM and Maria&Vitorino,	Rapid removal of the offending drug. UDCA may be beneficial in cholestatic DILI.	Mostly benign but may lead to acute liver failure requiring transplantation. Cholestasis may persist for months.	[69-72]
HLI	10%	Occurs in the setting of cardiac, respiratory or circulatory failure, typically in the first 48h after admission. Rapid rise in ALT/AST >20x ULN with return to baseline in one week. Cholestasis is seen in 1/3 of patients.	Clinical.	Correction of the underlying cause of ischemic injury. Circulatory and ventilatory support.	Depends on underlying comorbidities but mortality is >50%.	[26, 42, 73]

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase, DILI, drug-induced liver injury; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound GGT, gamma glutamyl transpeptidase; HLI, hypoxic liver injury; MRCP, magnetic resonance cholangiopancreatography; RUCAM, Roussel-Uclaf Causality Assessment Method; RUQ, right upper quadrant; TPN, total parenteral nutrition; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; US, ultrasound

Similarly to MRCP, early ERCP findings consist of intraductal filling defects of the intrahepatic bile ducts due to biliary casts. As the disease progresses, diffuse irregular strictures and dilations with the typical beaded appearance become evident. In later stages,

the peripheral intrahepatic bile ducts are completely obliterated leaving only a central biliary system that Leonhardt *et al.* described as a "pruned tree" [2, 9]. Concomitant extrahepatic bile duct involvement occurs in around 20% of the cases but it is always mild. In 6% of the cases the strictures are confined to the extrahepatic bile ducts [2, 30]. During ERCP it is important to collect bile samples for microbiological examination since in 98% of patients, a pathogen is identified, allowing for guided antimicrobial therapy [6].

The differential diagnosis based on radiographic findings includes PSC and other forms of SSC. Differentiation between SSC-CIP and other forms of sclerosing cholangitis heavily relies on the clinical history which allows for the identification of the primary insult. However, some radiological features suggest SSC-CIP, namely: sparing of the extrahepatic bile ducts and the presence of biliary casts [2, 74]. In fact, biliary casts seem to be exclusive to SSC-CIP and ischemic sclerosing cholangitis [2, 41]. Ischemic sclerosing cholangitis is mostly associated with post-OLT hepatic artery thrombosis and hepatic arterial infusion of floxuridine in the context of colorectal liver metastases [29]. **The different forms of SSC and their typical features are shown in Table 2.**

- **Histopathology**

Liver histology has limited diagnostic value because the early features are nonspecific changes and consistent with chronic bile duct obstruction [9]. Liver biopsies revealed findings suggestive of SSC-CIP in only 36% of patients in one study [30]. Furthermore, there seems to be no correlation between histological findings and laboratory values. Nonetheless, liver biopsies aid in the differential diagnosis of SSC-CIP, by excluding other conditions [32].

Histological findings can be divided into those affecting the portal/periportal areas and those affecting the acini. In the early stages only the portal/periportal areas are affected with biopsies showing oedema of the small and medium portal tracts, mild inflammatory infiltrates consisting mostly of lymphocytes with occasional neutrophils and cytological changes in the interlobular bile ducts (cytoplasmic vacuolization and loss of polarization) [9, 32]. As the disease progresses, marginal ductular proliferation, ductular metaplasia of periportal hepatocytes and portal/periportal fibrosis are observed. Bile thrombi can be seen in some patients [9, 13, 32]. Only in later stages are the acini affected, with biopsies revealing bilirubinostasis, hepatocellular rosette formation and cholestatic necrosis. Eventually, it can progress to biliary fibrosis and secondary biliary cirrhosis [75]. Esposito *et al.* hypothesized

that damage to the portal bile ducts is the primary insult and leads to inflammation and ductular proliferation in the portal/periportal area, while the parenchymal changes are the ultimate consequence of this process [32].

Table 2. Different forms of secondary sclerosing cholangitis with typical clinical and imagiological findings.

Etiology	Cause	Clinical features	US/CT scan	ERCP/MRCP	References
Obstructive	• Choledocholithiasis • Neoplasia • Gastroduodenal/hepatic arterial aneurysms • Biliary strictures following surgical trauma	May occur recurrent/ persistent bacterial cholangitis. Increased bilirubin.	Dilated bile ducts. CBD stones. Pancreatic or cholangiocarcinoma.	Intraductal stones. Evidence of extrinsic compression.	[29, 41]
Infectious	AIDS colangiopathy: • Cryptosporidiasis • CMV • Microsporidiasis	CD4+ <100/mm^3 Other opportunistic infections. HAART with restoration of immune function is the only treatment, antimicrobials are ineffective.	Intra and/or extrahepatic bile duct dilation. Hyperechoic echogenic nodules at the distal end of the CBD.	Papillary stenosis. Typical beaded appearance is seen in 20%.	[29, 76]
Immunologic	IgG4-Related disease	↑ serum IgG4 Associated with type 1 autoimmune pancreatitis in 90%. Responds to glucocorticoids.	Bile duct wall thickening. Pancreatic enlargement or other findings of IgG4-related disease.	Dilation following long and continuous stricture (>10mm). Narrowing of the main pancreatic duct.	[77, 78]
Ischemic	• Post-OLT hepatic artery thrombosis • Hepatic intra-arterial chemotherapy (TACE)	Liver transplanted patients. Liver metastases in patients with colorectal cancer. BCLC stage B hepatocellular carcinoma.	Dilated bile ducts. US may reveal bilomas.	Biliary casts. Middle third of the common bile duct > hepatic duct confluence > intrahepatic bile ducts.	[11, 29]
Drug-induced	• Amoxicilin-clavulanate • Ketamine • Celecoxib • Others	Extra-hepatic manifestations of intolerance. Mostly reversible with discontinuation of the offending drug.	Dilated bile ducts. Hydronephrosis is commonly seen in ketamine abuse.	Mainly right, left and common hepatic duct involvement.	[21, 41, 47]
Critically-ill patients	Ischemic bile duct injury	Persistent cholestasis in patients surviving ICU treatment.	US is normal in >50% of cases. CT and US may reveal intrahepatic bile duct dilation.	Sparing of the extrahepatic bile ducts. Biliary casts. "Pruned tree" appearance.	[2, 74]

BCLC, Barcelona clinic liver cancer; CBD, common bile duct; CMV, Cytomegalovirus; CT, computed tomography; HAART, highly active antiretroviral therapy; OLT, orthotopic liver transplantation; TACE, transarterial chemoembolization; US, ultrasound

Natural history of disease and prognosis

Persistent cholestasis in patients surviving a life-threatening event is what clinically defines SSC-CIP [13]. Despite having an unspecific presentation early on, SSC-CIP can have a dramatic course with mortality rates reaching 50% during ICU treatment. Mortality associates

with necessity for renal replacement therapy and higher MELD scores [30, 33]. The cause for admission in the ICU also affects mortality rates with burns and trauma in previously healthy patients associating with better outcomes in the ICU [27].

Typical sclerosing cholangitis manifestations, such as jaundice, pruritus and abdominal discomfort are only seen in patients who survive the ICU period, when the disease has progressed [29]. Severe unintentional weight loss is seen in most patients within the first year with an average loss of 18kg, in contrast with PSC where weight loss only occurs in one third of the patients [2, 79]. Recurrent episodes of bacterial cholangitis secondary to bile duct destruction are common, in which the peripheral bile duct branches can lose their connection to the central bile duct system, impairing bile flow and limiting the effect of antibiotic treatment. This disconnection favours the formation of cholangitic liver abscesses and increases the risk of biliary sepsis, an important cause of death in these patients [2, 34].

Progression to liver cirrhosis can occur rapidly over a period of months [2, 13]. In some patients it takes as little as weeks for the diagnosis of liver cirrhosis to be made [31]. This rapid progression translates into an exceptionally high mortality. The transplant-free survival is 55% after 1 year and only 14% after 6 years. SSC-CIP median transplant-free survival is 13-44 months, which contrasts with 89 months for PSC and 72 months for SSC in general [2, 34, 35]. On the other hand, while in PSC cholangiocarcinoma occurs in 7-13% of patients, there are no reports of cholangiocarcinoma in SSC-CIP patients [35, 39, 80, 81]. This might be explained by the short life expectancy and the short follow-up in the studies so far.

The most common cause of death is hepatic failure, which occurs in 36% of patients. Out of the 60% of surviving patients, approximately 40% develop biliary cirrhosis and remain in a stable condition, while the other 20% progress to end-stage liver disease requiring liver transplantation [5].

Treatment

Endoscopic removal of biliary casts and sphincterotomy improve biliary drainage and lead to a temporary clinical and biochemical improvement, even when biliary cirrhosis has already occurred [9, 36, 37]. Endoscopic balloon dilation and intermittent stenting of dominant stenoses also seem to improve cholestasis. However, in most cases this approach is not feasible because of the multifocal and intrahepatic localization of the stenoses [13, 36, 37].

Repeated endoscopic interventions are often necessary as biliary casts may recur [2, 43, 74]. Despite the transient improvement, disease progression seems inevitable and the outcome of patients is not affected by endoscopic therapy [32, 34].

Ursodeoxycholic acid (UDCA) is commonly used in an effort to improve bile flow [9, 36, 37, 43, 74]. No controlled studies assessing the therapeutic potential of UDCA in SSC-CIP have been carried out, but its efficacy seems to be limited [13, 34].

Recurrent episodes of cholangitis are treated with endoscopic therapy to alleviate obstruction and antimicrobials. The antimicrobial therapy should be adjusted based on microbiological analysis and it should be extended for 2 weeks [6, 38]. In many cases biliary drainage is inadequate because CPRE cannot access excluded peripheral bile ducts, limiting the effectiveness of the treatment [2].

When SSC-CIP progresses and biliary cirrhosis develops, OLT is the only curative option [36]. In some cases, urgent liver transplantation is required during ICU stay due to acute liver failure [9]. Up to 75% of SSC-CIP patients must be placed on the waiting list for liver transplantation within the first year after the diagnosis [2]. The MELD score is widely used in Europe to guide the allocation of liver grafts and has prognostic value in SSC-CIP [30, 82]. However, MELD alone may not be a good measurement of the urgency for liver transplantation, since many patients with SSC-CIP maintain stable coagulation and liver function despite a dismal evolution, thus delaying transplantation [33]. In the case of PSC, recurrent bacterial cholangitis confers higher priority in the form of MELD exception points [83]. In a study by Leonhardt *et al.*, 2 out of 16 patients died of biliary sepsis while on the transplant waiting list, so probably the same rationale should be applied for SSC-CIP [2]. Survival rates after liver transplant are comparable to those of patients transplanted due to alcoholic liver cirrhosis with 1-and 3-year survival rates around 90% and 85%, respectively [2, 33]. Most deaths post liver transplantation occur within the first year, being sepsis the main cause of death. Traumatic patients seem to have a better prognosis after liver transplant, due to being healthy prior to the life-threatening event [31].

Conclusion

SSC-CIP is a recently recognized, underdiagnosed entity that poses a great challenge to both intensivists and gastroenterologists. In SSC-CIP both critical illness and ICU treatment are

responsible for ischemic injury of the biliary tree that, together with changes in bile composition, leads to the formation of biliary casts and stricturing, with subsequent persistent bacterial infection driving the rapid progression of the disease. Importantly, high-dose vasopressor use does not seem to be associated with the development of SSC-CIP. SSC-CIP shows a typical cholestatic pattern that persists after recovery from the critical illness, which should be a hint to differentiate from other causes of cholestasis in the ICU. The diagnosis requires MRCP/ERCP but it is often delayed due to the difficulty in assessing which patients will benefit from these exams. SSC-CIP has a dismal prognosis with high mortality rates even during the ICU and rapid progression to liver cirrhosis requiring liver transplantation. Medical treatment is lacking, and endoscopic interventions allow only for palliative treatment, hence the diagnosis of SSC-CIP should prompt early referral for liver transplantation.

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References

1. Scheppach, W., G. Druge, G. Wittenberg, J.G. Mueller, et al. (2001) Sclerosing cholangitis and liver cirrhosis after extrabiliary infections: Report on three cases. Critical Care Medicine 29:438-441.
2. Leonhardt, S., W. Veltzke-Schlieker, A. Adler, E. Schott, et al. (2015) Secondary Sclerosing Cholangitis in Critically Ill Patients: Clinical Presentation, Cholangiographic Features, Natural History, and Outcome: A Series of 16 Cases. Medicine (Baltimore) 94:e2188.
3. Leonhardt, S., W. Veltzke-Schlieker, A. Adler, E. Schott, et al. (2015) Trigger mechanisms of secondary sclerosing cholangitis in critically ill patients. Critical Care 19:131.
4. Schade, I., D. Radakovic, J. Hoffmann, S.P. Sommer, et al. (2017) Secondary sclerosing cholangitis in cardiac surgical patients: A complication with a dismal prognosis. Journal of Thoracic and Cardiovascular Surgery 154:906-912.
5. Lin, T., K. Qu, X. Xu, M. Tian, et al. (2014) Sclerosing cholangitis in critically ill patients: an important and easily ignored problem based on a German experience. Frontiers in Medicine 8:118-26.
6. Kirchner, G.I. and P. Rummele. (2015) Update on Sclerosing Cholangitis in Critically Ill Patients. Viszeralmedizin 31:178-84.
7. Weig, T., M.I. Schubert, N. Gruener, M.E. Dolch, et al. (2012) Abdominal obesity and prolonged prone positioning increase risk of developing sclerosing cholangitis in critically ill patients with influenza A-associated ARDS. European Journal of Medical Research 17:30-30.
8. Trauner, M., P. Fickert, and M. Wagner. (2007) MDR3 (ABCB4) defects: a paradigm for the genetics of adult cholestatic syndromes. Seminars in Liver Disease 27:77-98.
9. Gelbmann, C.M., P. Rummele, M. Wimmer, F. Hofstadter, et al. (2007) Ischemic-like cholangiopathy with secondary sclerosing cholangitis in critically ill patients. American Journal of Gastroenterology 102:1221-9.
10. Kobayashi, S., Y. Nakanuma, and O. Matsui. (1994) Intrahepatic peribiliary vascular plexus in various hepatobiliary diseases: A histological survey. Human Pathology 25:940-46.
11. Deltenre, P. and D.C. Valla. (2008) Ischemic cholangiopathy. Seminars in Liver Disease 28:235-46.
12. Sakr, Y., K. Reinhart, J.L. Vincent, C.L. Sprung, et al. (2006) Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study. Critical Care Medicine 34:589-97.
13. Benninger, J., R. Grobholz, Y. Oeztuerk, C.H. Antoni, et al. (2005) Sclerosing cholangitis following severe trauma: description of a remarkable disease entity with emphasis on possible pathophysiologic mechanisms. World Journal of Gastroenterology 11:4199-205.
14. Putensen, C., H. Wrigge, and R. Hering. (2006) The effects of mechanical ventilation on the gut and abdomen. Current Opinion in Critical Care 12:160-165.
15. Paramythiotis, D., P. Kazamias, V. Grosomanidis, and K. Kotzampassi. (2008) Splanchnic ischemia during mechanical ventilation. Annals of Gastroenterology 21:45-52.
16. Shah and J. (2003) Biliary casts after orthotopic liver transplantation: clinical factors, treatment, biochemical analysis. The American Journal of Gastroenterology 98:1861-1867.
17. Fickert, P., A. Fuchsbichler, M. Wagner, G. Zollner, et al. (2004) Regurgitation of bile acids from leaky bile ducts causes sclerosing cholangitis in Mdr2 (Abcb4) knockout mice. Gastroenterology 127:261-274.
18. Fouassier, L., M. Beaussier, E. Schiffer, C. Rey, et al. (2007) Hypoxia-induced changes in the expression of rat hepatobiliary transporter genes. American Journal of Physiology-Gastrointestinal and Liver Physiology 293:G25-G35.
19. Spirlì, C., M.H. Nathanson, R. Fiorotto, E. Duner, et al. (2001) Proinflammatory Cytokines Inhibit Secretion in Rat Bile Duct Epithelium. Gastroenterology 121:156-169.

20. Voigtlander, T., E. Leuchs, R.P. Vonberg, P. Solbach, et al. (2015) Microbiological analysis of bile and its impact in critically ill patients with secondary sclerosing cholangitis. Journal of Infection 70:483-90.
21. Visentin, M., D. Lenggenhager, Z. Gai, and G.A. Kullak-Ublick. (2018) Drug-induced bile duct injury. Biochimica et Biophysica Acta - Molecular Basis of Disease 1864:1498-1506.
22. Gudnason, H.O., H.K. Bjornsson, M. Gardarsdottir, H.M. Thorisson, et al. (2015) Secondary sclerosing cholangitis in patients with drug-induced liver injury. Digestive and Liver Disease 47:502-7.
23. Padda, M.S., M. Sanchez, A.J. Akhtar, and J.L. Boyer. (2011) Drug-induced cholestasis. Hepatology 53:1377-87.
24. Turkish, A., J.J. Luo, and J.H. Lefkowitch. (2013) Ketamine abuse, biliary tract disease, and secondary sclerosing cholangitis. Hepatology 58:825-7.
25. Grau, T., A. Bonet, M. Rubio, D. Mateo, et al. (2007) Liver dysfunction associated with artificial nutrition in critically ill patients. Critical Care 11:R10.
26. Horvatits, T., M. Trauner, and V. Fuhrmann. (2013) Hypoxic liver injury and cholestasis in critically ill patients. Current Opinion in Critical Care 19:128-32.
27. Laurent, L., C. Lemaitre, A. Minello, A. Plessier, et al. (2017) Cholangiopathy in critically ill patients surviving beyond the intensive care period: a multicentre survey in liver units. Alimentary Pharmacology & Therapeutics 46:1070-1076.
28. Aronsohn, A. and D. Jensen. (2011) Hepatobiliary manifestations of critically ill and postoperative patients. Clinical Liver Disease 15:183-97.
29. Ruemmele, P., F. Hofstaedter, and C.M. Gelbmann. (2009) Secondary sclerosing cholangitis. Nature Reviews Gastroenterology & Hepatology 6:287-95.
30. Voigtlander, T., A.A. Negm, A.S. Schneider, C.P. Strassburg, et al. (2012) Secondary sclerosing cholangitis in critically ill patients: model of end-stage liver disease score and renal function predict outcome. Endoscopy 44:1055-8.
31. Kirchner, G.I., M.N. Scherer, A. Obed, P. Ruemmele, et al. (2011) Outcome of patients with ischemic-like cholangiopathy with secondary sclerosing cholangitis after liver transplantation. Scandinavian Journal of Gastroenterology 46:471-8.
32. Esposito, I., A. Kubisova, A. Stiehl, H. Kulaksiz, et al. (2008) Secondary sclerosing cholangitis after intensive care unit treatment: clues to the histopathological differential diagnosis. Virchows Archiv 453:339-45.
33. Voigtlander, T., E. Jaeckel, F. Lehner, M.P. Manns, et al. (2015) Liver transplantation for critically Ill patients with secondary sclerosing cholangitis: Outcome and complications. Liver Transplantation 21:1295-9.
34. Kulaksiz, H., D. Heuberger, S. Engler, and A. Stiehl. (2008) Poor outcome in progressive sclerosing cholangitis after septic shock. Endoscopy 40:214-8.
35. Gossard, A.A., P. Angulo, and K.D. Lindor. (2005) Secondary sclerosing cholangitis: a comparison to primary sclerosing cholangitis. American Journal of Gastroenterology 100:1330-3.
36. Engler, S., C. Elsing, C. Flechtenmacher, L. Theilmann, et al. (2003) Progressive sclerosing cholangitis after septic shock: a new variant of vanishing bile duct disorders. Gut 52:688-693.
37. Jaeger, C., G. Mayer, R. Henrich, L. Gossner, et al. (2006) Secondary sclerosing cholangitis after long-term treatment in an intensive care unit: Clinical presentation, endoscopic findings, treatment, and follow-up. Endoscopy 38:730-734.
38. Zimmer, V. and F. Lammert. (2015) Acute Bacterial Cholangitis. Viszeralmedizin 31:166-72.
39. Williamson, K.D. and R.W. Chapman. (2015) Primary sclerosing cholangitis: a clinical update. British Medical Bulletin 114:53-64.
40. Mohammad Alizadeh, A.H., A. Shahnazi, A. Rasoulzadeh, E. Shams, et al. (2012) Characteristic Findings of Primary Sclerosing Cholangitis on Endoscopic Retrograde

Cholangiography: Which is the Most Common Finding? Clinical Medicine Insights: Gastroenterology 5:1-4.
41. Brooling, J. and R. Leal. (2017) Secondary Sclerosing Cholangitis: a Review of Recent Literature. Current Gastroenterology Reports 19:44.
42. Jenniskens, M., L. Langouche, and G. Van den Berghe. (2018) Cholestatic Alterations in the Critically Ill: Some New Light on an Old Problem. Chest 153:733-743.
43. Reichert, M.C., C. Jungst, F. Grunhage, F. Lammert, et al. (2016) Secondary sclerosing cholangitis rapidly leading to liver cirrhosis: a possible post-ICU treatment sequel. QJM: An International Journal of Medicine 109:119-20.
44. Zack, F., H. Nizze, V. Blaas, A. Port, et al. (2018) Secondary sclerosing cholangitis in critically ill patients after a traffic accident-a new entity that should be considered in death classification. International Journal of Legal Medicine 132:1729-1732.
45. Gudnason, H.O. and E.S. Bjornsson. (2017) Secondary sclerosing cholangitis in critically ill patients: current perspectives. Clinical and Experimental Gastroenterology 10:105-111.
46. Molodecky, N.A., H. Kareemi, R. Parab, H.W. Barkema, et al. (2011) Incidence of primary sclerosing cholangitis: a systematic review and meta-analysis. Hepatology 53:1590-9.
47. Lo R S C, K.R., Freeman J G, Austin A S. (2011) Cholestasis and biliary dilatation associated with chronic ketamine abuse: a case series. Singapore Medical Journal 52:52-55.
48. Douglass, T.C. and W.W. Cutter. (1948) Arterial blood supply of the common bile duct. Archives of Surgery 57:599-612.
49. Woolsey, C.A. and C.M. Coopersmith. (2006) Vasoactive drugs and the gut: Is there anything new? Current Opinion in Critical Care 12:155-59.
50. Di Giantomasso, D., C.N. May, and R. Bellomo. (2003) Norepinephrine and vital organ blood flow during experimental hyperdynamic sepsis. Intensive Care Medicine 29:1774-81.
51. Krejci, V., L.B. Hiltebrand, and G.H. Sigurdsson. (2006) Effects of epinephrine, norepinephrine, and phenylephrine on microcirculatory blood flow in the gastrointestinal tract in sepsis. Critical Care Medicine 34:1456-63.
52. Guérin, J.-P., J. Levraut, C. Samat-Long, X. Leverve, et al. (2005) Effects of Dopamine and Norepinephrine on Systemic and Hepatosplanchnic Hemodynamics, Oxygen Exchange, and Energy Balance in Vasoplegic Septic Patients. Shock 23:18-24.
53. FUJITA, Y. (1993) Effects of PEEP on splanchnic hemodynamics and blood volume. Acta Anaesthesiologica Scandinavica 37:427-431.
54. Gor, N.V., R.M. Levy, J. Ahn, D. Kogan, et al. (2008) Biliary cast syndrome following liver transplantation: Predictive factors and clinical outcomes. Liver Transplantation 14:1466-72.
55. Beuers, U., S. Hohenester, L.J. de Buy Wenniger, A.E. Kremer, et al. (2010) The biliary HCO(3)(-) umbrella: a unifying hypothesis on pathogenetic and therapeutic aspects of fibrosing cholangiopathies. Hepatology 52:1489-96.
56. Gotthardt, D., H. Runz, V. Keitel, C. Fischer, et al. (2008) A mutation in the canalicular phospholipid transporter gene, ABCB4, is associated with cholestasis, ductopenia, and cirrhosis in adults. Hepatology 48:1157-66.
57. Smit, J.J.M., A.H. Schinkel, R.P.J.O. Elferink, A.K. Groen, et al. (1993) Homozygous disruption of the murine MDR2 P-glycoprotein gene leads to a complete absence of phospholipid from bile and to liver disease. Cell 75:451-462.
58. Hoekstra, H., Y. Tian, W. Jochum, B. Stieger, et al. (2008) Dearterialization of the liver causes intrahepatic cholestasis due to reduced bile transporter expression. Transplantation 85:1159-66.
59. Robertson, C.M. and C.M. Coopersmith. (2006) The systemic inflammatory response syndrome. Microbes and Infection 8:1382-9.
60. Hoffmeister, B., J. Ockenga, G. Schachschal, N. Suttorp, et al. (2007) Rapid development of secondary sclerosing cholangitis due to vancomycin-resistant enterococci. Journal of Infection 54:e65-8.

61. Jungst, C., V. Stadlbauer, M.C. Reichert, V. Zimmer, et al. (2017) NOD2 gene variants confer risk for secondary sclerosing cholangitis in critically ill patients. Scientific Reports 7:7026.
62. Al Nabhani, Z., G. Dietrich, J.P. Hugot, and F. Barreau. (2017) Nod2: The intestinal gate keeper. PLOS Pathogens 13:e1006177.
63. Sinakos, E., G. Abbas, R.A. Jorgensen, and K.D. Lindor. (2012) Serum lipids in primary sclerosing cholangitis. Digestive and Liver Disease 44:44-8.
64. Molvar, C. and B. Glaenzer. (2016) Choledocholithiasis: Evaluation, Treatment, and Outcomes. Seminars in Interventional Radiology 33:268-276.
65. Chand, N. and A.J. Sanyal. (2007) Sepsis-induced cholestasis. Hepatology 45:230-41.
66. Brienza, N., L. Dalfino, G. Cinnella, C. Diele, et al. (2006) Jaundice in critical illness: promoting factors of a concealed reality. Intensive Care Medicine 32:267-274.
67. Strnad, P., F. Tacke, A. Koch, and C. Trautwein. (2017) Liver - guardian, modifier and target of sepsis. Nature Reviews Gastroenterology & Hepatology 14:55-66.
68. Copelan, A. and B.S. Kapoor. (2015) Choledocholithiasis: Diagnosis and Management. Techniques in Vascular and Interventional Radiology 18:244-55.
69. Alempijevic, T., S. Zec, and T. Milosavljevic. (2017) Drug-induced liver injury: Do we know everything? World Journal of Hepatology 9:491-502.
70. Kullak-Ublick, G.A., R.J. Andrade, M. Merz, P. End, et al. (2017) Drug-induced liver injury: recent advances in diagnosis and risk assessment. Gut 66:1154-1164.
71. Bjornsson, E.S., O.M. Bergmann, H.K. Bjornsson, R.B. Kvaran, et al. (2013) Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 144:1419-25, 1425 e1-3; quiz e19-20.
72. Wree, A., A. Dechene, K. Herzer, P. Hilgard, et al. (2011) Steroid and ursodesoxycholic Acid combination therapy in severe drug-induced liver injury. Digestion 84:54-9.
73. Lightsey, J.M. and D.C. Rockey. (2017) Current concepts in ischemic hepatitis. Current Opinion in Gastroenterology 33:158-163.
74. Kwon, O.N., S.H. Cho, C.K. Park, and S.H. Mun. (2012) Biliary cast formation with sclerosing cholangitis in critically ill patient: case report and literature review. Korean Journal of Radiology 13:358-62.
75. Pollheimer, M.J., P. Fickert, and B. Stieger. (2014) Chronic cholestatic liver diseases: clues from histopathology for pathogenesis. Molecular Aspects of Medicine 37:35-56.
76. Naseer, M., F.E. Dailey, A.A. Juboori, S. Samiullah, et al. (2018) Epidemiology, determinants, and management of AIDS cholangiopathy: A review. World Journal of Gastroenterology 24:767-774.
77. Kamisawa, T., Y. Zen, T. Nakazawa, and K. Okazaki. (2018) Advances in IgG4-related pancreatobiliary diseases. The Lancet Gastroenterology & Hepatology 3:575-585.
78. Zen, Y., H. Kawakami, and J.H. Kim. (2016) IgG4-related sclerosing cholangitis: all we need to know. Journal of Gastroenterology 51:295-312.
79. Wiesner, R.H., M. Grambsch, E. Rolland, B. Hunter, et al. (1989) Primary Sclerosing Cholangitis : Natural History , Prognostic Factors and Survival Analysis. Hepatology 10:430-436.
80. Rahman, M., H. Chapel, R.W. Chapman, and J.D. Collier. (2012) Cholangiocarcinoma complicating secondary sclerosing cholangitis from cryptosporidiosis in an adult patient with CD40 ligand deficiency: case report and review of the literature. International Archives of Allergy and Immunology 159:204-8.
81. Zhang, Y.A., X.Z. Shen, J.M. Zhu, and T.T. Liu. (2015) Extensive Metastatic Cholangiocarcinoma Associated With IgG4-Related Sclerosing Cholangitis Misdiagnosed as Isolated IgG4-Related Sclerosing Cholangitis: A Case Report and Literature Review. Medicine (Baltimore) 94:e2052.
82. European Association for the Study of the Liver. Electronic address, e.e.e. (2016) EASL Clinical Practice Guidelines: Liver transplantation. Journal of Hepatology 64:433-485.

83. Khungar, V. and D.S. Goldberg. (2016) Liver Transplantation for Cholestatic Liver Diseases in Adults. Clinical Liver Disease 20:191-203.